

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11) Publication number:

0 054 732
A1

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 81109391.3

(22) Date of filing: 30.10.81

(51) Int. Cl.²: **C 07 C 57/03, C 07 C 69/587,**
C 07 C 103/133, A 61 K 31/19,
A 61 K 31/23, A 61 K 31/16

(30) Priority: 24.12.80 JP 182115/80

(43) Date of publication of application: 30.06.82
Bulletin 82/26

(84) Designated Contracting States: BE CH DE FR GB IT LI
NL SE

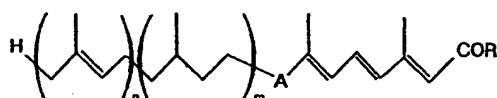
(71) Applicant: Eisai Co., Ltd., 6-10, Koishikawa 4-chome
Bunkyo-ku, Tokyo 112 (JP)

(72) Inventor: Yamatsu, Isao, 1-14-39-509, Kamiakki-cho,
Kawaguchi-shi Saitama (JP)
Inventor: Inai, Yuichi, Tokyu Hasune Haitsu, 3-11-25-702,
Hasune Itabashi-ku, Tokyo (JP)
Inventor: Abe, Shinya, 3-2-5, Nakamura, Nerima-ku,
Tokyo (JP)
Inventor: Suzuki, Takeshi, 144-10, Wakamatsu, Abiko-shi
Chiba (JP)
Inventor: Suzuki, Yoshikazu, 6, Aza Sakuranosato
Kouda, Asai-cho Ichinomiya-shi Aichi (JP)
Inventor: Tagaya, Osamu, 1648-13, Kano, Gifu-shi Gifu
(JP)
Inventor: Suzuki, Kouichi, 1-59, Ozakikitamachi,
Kakamigahara-shi Gifu (JP)
Inventor: Abe, Kouichi, 3-52-7, Yotsuya, Fuchu-shi Tokyo
(JP)
Inventor: Yamada, Kouji, 1-21-17, Tokiwadai, Itabashi-ku
Tokyo (JP)

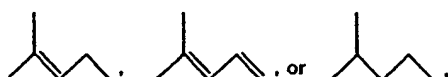
(74) Representative: Hansen, Bernd, Dr.rer.nat. et al,
Hoffmann . Eitle & Partner Patentanwälte
Arabellastrasse 4, D-8000 München 81 (DE)

(54) Conjugated polyprenylcarboxylic acids and their derivatives as well as pharmaceutical preparations containing these compounds.

(57) A conjugated polyprenylcarboxylic acid and its derivative having the formula:



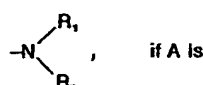
in which each of n and m is 0, 1 or 2, n + m is 1 or 2, A is



and R is a hydroxyl group, a lower alkoxy group or

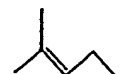


wherein each of R₁ and R₂ represents a hydrogen atom, a lower alkyl group, or an aryl group; provided that R is



n is 1 and m is 0.

There are also described pharmaceutical preparations containing above compounds.



EP 0 054 732 A1

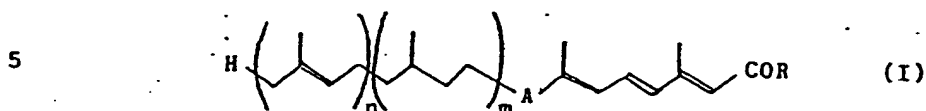
BEST AVAILABLE COPY

0054732


- 1 -

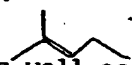
Conjugated polyprenylcarboxylic acids and their derivatives
as well as pharmaceutical preparations containing these compounds

This invention relates to novel conjugated polyprenylcarboxylic acids and their derivatives having the formula (I):



in which each of n and m is 0, 1 or 2, $n + m$ is 1 or 2, A is

10 , and R is a hydroxyl group, a lower alkoxy group or $-N \begin{smallmatrix} R_1 \\ R_2 \end{smallmatrix}$ wherein each of R_1 and R_2 represents a hydrogen atom, a lower alkyl group, or an aryl group; provided R is $-N \begin{smallmatrix} R_1 \\ R_2 \end{smallmatrix}$, if A is

15 , n is 1 and m is 0.
 as well as pharmaceutical preparations containing these compounds

Examples of the lower alkoxy groups represented by R in the above-mentioned formula (I) include methoxy, ethoxy, i-propoxy, n-propoxy, t-butoxy and n-butoxy. Examples of the lower alkyl groups represented by R_1 and R_2 include methyl, ethyl, i-propyl, n-propyl, t-butyl and n-butyl, and examples of the aryl groups represented by R_1 and R_2 include phenyl and a phenyl group having substituent groups such as hydroxyl, a lower alkyl group or halogen. If R in the formula (I) is hydroxyl, the compound may be in the form of a salt such as sodium or potassium salt.

W. Bollag, et al. reported in Europ. J. Cancer, Vol. 10, p 731 (1974) that retinoids such as ethyl 9-(2,3,6-trimethyl-4-methoxyphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoate have anti-cancer activity. These retinoid compounds, however, are highly toxic, and further have problems such as causing hypervitaminosis of Vitamin A when administered.

The polyprenylcarboxylic acids and their derivatives of the formula (I) show remarkable anti-cancer activity and are highly safe compounds. For instance, these polyprenylcarboxylic

0054732

- 2 -

acids and their derivatives do not cause hypervitaminosis of Vitamin A. Further toxicities of the polyprenylcarboxylic acids and their derivatives of the formula (I) other than the hypervitaminosis are also at low level.

Moreover, the polyprenylcarboxylic acids and their derivatives of the formula (I) are of value as therapeutic agents for treatment of skin diseases with keratinization or treatment of allergic or inflammatory skin diseases, such as psoriasis, acne, acne vulgaris, Darier's disease, palmo-plantar pustulosis, lichen plasnus, ichthyosis, erythroderma, pityriasis rubra pilasus, and keratosis senilis, as well as the therapeutic agents for prevention and treatment of cancer and precancerous conditions.

The conjugated polyprenylcarboxylic acid and its derivative of the formula (I) can be prepared by the following processes.

Process A

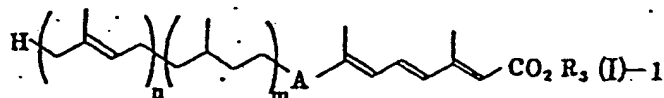
(1) A compound having the formula (II):



in which n , m and A have the same meanings as defined hereinbefore, and a Wittig reagent derived from a compound having the formula (III):



in which X represents a halogen atom, and R_3 represents a lower alkyl group, are reacted to give the polyprenylcarboxylic acid derivative having the formula (I) - 1:

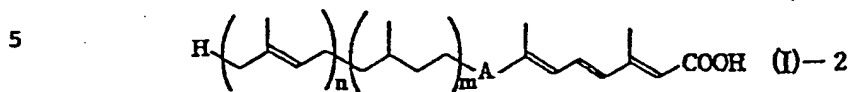


in which n , m , A and R_3 have the same meanings as defined above.

- 3 -

0054732

(2) The polyprenylcarboxylic acid derivative of the formula (I) - 1, if desired, can be hydrolyzed to give the polyprenylcarboxylic acid having the formula (I) - 2:



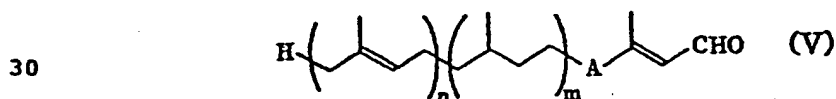
in which n , m and A have the same meanings as defined above.

10 Examples of the Wittig reagents employed in the above-described (1) stage and derived from a compound of the formula (III) include phosphoric compounds produced by the reaction between the compound of the formula (III) and triphenylphosphine, phenyldialkoxyposphine, trialkylphosphite, or the like. The preparation of the reagent and the wittig reaction
15 employing the reagent can be carried out by the conventional methods such as the method given by Wadworth, et al. in J. Am. Chem. Soc., Vol. 83, p. 1733 (1961), the method given by Greenwald, et al. in J. Org. Chem., Vol. 28, p. 1128 (1963),
20 and the method given by Horner, et al. in Ber., Vol. 95, p. 581 (1962).

In the above-described (2) stage, the hydrolysis can be carried out in the presence of a base generally employed for hydrolysis of carboxylic acid esters, such as sodium hydroxide and potassium hydroxide.

25 Process B

(1) A compound having the formula (V):

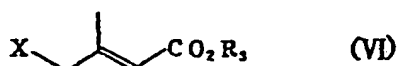


in which n , m and A have the same meanings as defined hereinbefore, and a Wittig reagent derived from a compound having the formula (VI):

35

0054732

- 4 -



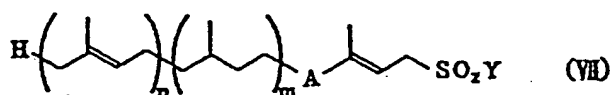
in which X and R_3 have the same meanings as defined above, are reacted to give the polyprenylcarboxylic acid derivative having the above-mentioned formula (I) - 1.

(2) The polyprenylcarboxylic acid derivative of the formula (I) - 1, if desired, can be hydrolyzed to give the polyprenylcarboxylic acid having the above-mentioned formula (I) - 2.

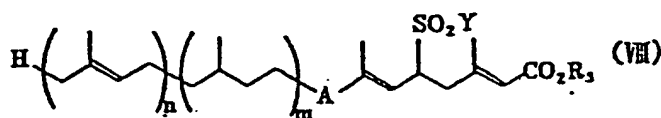
Each of the procedures in the above-described stages (1) and (2) can be carried out in the same manner as in Process A.

Process C

(1) A compound having the formula (VII):



in which n , m and A have the same meanings as defined hereinbefore, and Y represents a lower alkyl group or an aryl group, and the compound of the above-mentioned formula (VI) are reacted to give a compound having the formula (VIII):



in which n , m , A, Y and R_3 have the same meanings as defined above; and then

(2) the compound of the formula (VIII) is subjected to a reaction for removal of the sulfinic acid group and hydrolysis in the presence of a base to give the compound of the aforementioned formula (I) - 2.

The above-mentioned stage (1) is carried out in the

0054732

- 5 -

presence of a base. Examples of the bases include n-butyl-lithium and phenyllithium. Examples of the reaction solvents include tetrahydrofuran, diethyl ether and 1,2-dimethoxyethane. The reaction is generally carried out at a temperature lower than room temperature.

The above-mentioned stage (2) can be carried out in the same manner as the stage (2) of the aforementioned Process A.

If the polyprenylcarboxylic acid derivative in the amide form is desired, the polyprenylcarboxylic acid of the formula (I) - 2 obtained in one of the Processes A, B and Q is reacted with a compound having the formula (IX):



in which R_1 and R_2 have the same meanings as defined hereinbefore, to give the desired amide derivative that is, also; included in the polyprenylcarboxylic acid derivative of the invention. The above-described reaction is preferably carried out in the presence of a condensation reagent such as ethyl chlorocarbonate.

Examples of the polyprenylcarboxylic acids and their derivatives of the formula (I) according to the invention include:

3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosaheptaenoic acid

3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoic acid

3,7,11,15-tetramethyl-2,4,6-hexadecatrienoic acid

3,7,11,15-tetramethyl-2,4,6,8,10,14-hexadecahexaenoic acid

3,7,11,15-tetramethyl-2,4,6,10-hexadecatetraenoic acid

3,7,11,15,19-pentamethyl-2,4,6,8,10,14,18-eicosaheptaenoic acid

3,7,11,15,19-pentamethyl-2,4,6,10,18-eicosapentaenoic acid

ethyl 3,7,11,15-tetramethyl-2,4,6-hexadecatrienoate

0054732

- 6 -

ethyl 3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosa-
hexaenoate

methyl 3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosa-
hexaenoate

5 ethyl 3,7,11,15-tetramethyl-2,4,6,8,10,14-hexadeca-
enoate

3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoamide
N-(3'-hydroxyphenyl)-3,7,11,15-tetramethyl-2,4,6,10,14-
hexadecapentaenoamide

10 N-ethyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapenta-
enoamide

N,N-dimethyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadeca-
pentaenoamide

15 N-ethyl-3,7,11,15-tetramethyl-2,4,6,8,10,14-hexadeca-
hexaenoamide

N-ethyl-3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosa-
hexaenoamide

20 The results of the pharmacological tests and toxicity
tests on the polyprenyl compounds of the formula (I) are set
forth below.

Pharmacological Tests (Anti-cancer Activity)

(1) Test procedure

25 A mouse (ICR strain, female, 60 days age) was shaved at
the back of neck (to the extent of 5 cm²). 7,12-dimethylbenzol-
[2]-anthracene was dissolved in acetone to give 75 mg / 100 ml.
solution. The so prepared solution was applied to the mouse
on the 60th day of age and further on the 75th day of age in the
amount of 0.2 ml per mouse.

30 Croton oil was dissolved in acetone to give 250 mg /
100 ml solution, and the so prepared solution was applied
to the mouse in the amount of 0.2 ml per mouse, twice a
week until the treatment was started. When 3 - 7 papillomata
35 (diameter of 3 - 8 mm for each, and total diameter of 30 -
60 mm) were produced for a mouse, the treatment was started.

0054732

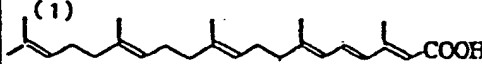
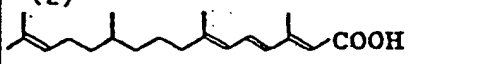
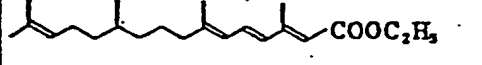
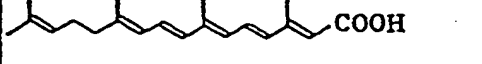
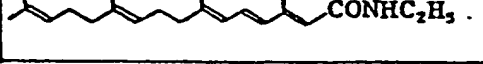
- 7 -

The compound to be tested (test compound) was dissolved in groundnut oil to give 20 mg /ml solution, and administered orally to the mouse. The solution was administered 10 times for 14 days (once a day), and the diameters of the papillomata were measured on the 14th day to determine the total diameter for each mouse. Ratio of increase or decrease of the papillomata was calculated from the total diameter on the 14th day and the total diameter measured prior to

the starting of administration of the test compound. This value was adopted for evaluating the anti-cancer activity.

(2) Results

Table 1

Test Compound	Number of mouse	Ratio of increase or decrease of papillomata (%)
Groundnut only (Control)	3	+1 7.1
(1) 	5	-2 4.0
(2) 	4	-1 9.5
(3) 	4	-1 0.2
(4) 	5	-2 6.3
(5) 	5	-2 5.5

- 8 -

0054732

Remarks: The compounds identified by the structural formulae in Table 1 correspond to the following polyprenyl compounds.

- 5
- (1) 3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosahexaenoic acid
- (2) 3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoic acid
- (3) ethyl 3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoate
- 10
- (4) 3,7,11,15-tetramethyl-2,4,6,8,10,14-hexadecaheptaenoic acid
- (5) 3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenamide

15

As seen from the data in Table 1, the polyprenyl compounds of the formula (I) are effective against the papilloma.

Toxicity Tests

(1) Test procedure

20

The test compound was administered repeatedly to a group of 6 mice (ICR strain, female) for 14 days in the dosage of 200 mg /kg /day. In the course of the administration procedures, increase or decrease of the weight of the mouse, occurrence of death, etc. were observed.

(2) Test compound

25

The compounds set forth in the above Table 1 were employed.

(3) Test results

30

No death was observed. Decrease of the weight was not observed, and a little increase of the weight was observed. No symptoms indicating the effects of side actions, such as hair loss, cyanosis, etc., were observed.

35

The decrease of the weight and hair loss are known as indicating the hypervitaminosis of Vitamin A. Accordingly, the results are considered to indicate that the polyprenyl compounds of the formula (I) do not cause the hypervitaminosis of Vitamin A.

- 9 -

0054732

In view of the pharmacological test results and the toxicity test results as described hereinbefore, the poly-prenyl compounds of the formula (I) are judged to be of high safety and to be of value as anti-cancer agents for prevention and treatment of cancer and precancerous conditions.

For the application as the anti-cancer agent, the poly-prenyl compound of the formula (I) can be administered orally in the form of powder, granule, pellet, hard capsule, etc., or parenterally in the form of ointment, suppository, injection solution, etc. The dosage is generally set in the range of 40 mg to 4 g /day for an adult. If the polyprenyl compound of the formula (I) is applied in the form of an external preparation, the dosage can be varied depending on the largeness of area on the affected part. The above-mentioned preparations can be prepared from the polyprenyl compound and generally employable carriers for the medical use by utilizing the conventional methods.

The following examples will illustrate processes for the preparations of the polyprenylcarboxylic acids and their derivatives of the formula (I) according to the invention, but these examples are not given to restrict the invention.

- 10 -

0054732

Example 1Ethyl 3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoate

To a suspension of 2.5 g. of 55 % sodium hydride (in oil) in 30 ml. of n-hexane was added 13.6 g. of triethyl phosphonoacetate. The mixture was then heated under reflux, and 10 g. of 6,10,14-trimethyl-3,5,13-pentadecatrien-2-on was added dropwise to the mixture under stirring. After 30 minutes, the reaction liquid was poured into 100 ml. of ice-water, and then 200 ml. of n-hexane was added for extraction. The n-hexane phase was separated, washed with two 50 ml. portions of a mixture of methanol and water (2 : 1), and concentrated. The so obtained concentrate was purified by the silica gel column chromatography to give 9.0 g. of the desired product as an oil.

Analysis for $C_{22}H_{36}O_2$

	C	H
Calculated (%)	79.46	10.92
Found (%)	79.74	11.04

NMR spectrum (δ , $CDCl_3$): 0.87 (3H, d, J = 6Hz), 1.28 (3H, t, J = 7Hz), 1.0 - 1.6 (7H), 1.61 (3H, s), 1.69 (3H, s), 1.85 (3H, s), 1.9 - 2.4 (4H), 23.4 (3H, d, J = 1Hz), 4.17 (2H, q, J = 7Hz), 5.10 (1H, t, J = 7Hz), 5.75 (1H, bs), 5.95 (1H, d, J = 11Hz), 6.16 (1H, d, J = 15Hz), 6.86 (1H, dd, J = 15Hz, 11Hz)

Mass spectrum (m/e): 332 (M^+)

30

0054732

- 11 -

Example 23,7,11,15-Tetramethyl-2,4,6,14-hexadecatetraenoic acid

8.0 g. of the ethyl 3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoate obtained in the previous :

5 Example 1 was added ^{to} a solution of 3.2 g. of potassium hydroxide in 20 ml. of isopropyl alcohol, and the mixture was stirred at 50 °C for 1 hour. The reaction liquid was then poured into ice-water, made acidic by addition of hydrochloric acid, and extracted with 50 ml. of diethyl ether. The ether phase was
10 washed with water, dried over magnesium sulfate, and concentrated to give 7. g. of an oil. The oil was dissolved in 40 ml. of n-hexane and crystallized at - 20°C to give 3.1 g. of the desired product as white crystals.

M.p. : 60 - 62 °C

15 Analysis for $C_{20}H_{32}O_2$

	C	H
Calculated (%)	78.89	10.59
Found (%)	78.77	10.63

20 NMR spectrum (δ , $CDCl_3$): 0.87 (3H, d, J = 6Hz), 1.0 - 1.6 (7H), 1.60 (3H, s), 1.69 (3H, s), 1.85 (3H, s), 1.9 - 2.3 (4H), 2.34 (3H, d, J = 1Hz), 5.10 (1H, t, J = 7Hz), 5.77 (1H, bs), 5.97 (1H, d, J = 11Hz), 6.20 (1H, d, J = 15Hz), 6.91 (1H, dd, J = 15Hz, 11Hz), 9.6 (1H, b)

25 Mass spectrum (m/e): 304 (M^+)

Example 33,7,11,15-Tetramethyl-2,4,6,8,10,14-hexadecaheptaenoic acid

30 To a suspension of 30.3 g. of sodium ethoxide in 300 ml. of tetrahydrofuran was added 118 g. of diethyl 3-ethoxycarbonyl-2-methyl-2-propenylphosphonate. To the mixture was added 67 g. of 3,7,11-trimethyl-2,4,6,10-dodecatetraen-1-al under stirring, chilling with ice and shielding from the light.
35 After 1 hour, the reaction liquid was poured into 1 liter of water, and 1 liter of n-hexane was added for extraction.

0054732

- 12 -

The n-hexane phase was separated, washed with two 100 ml. portions of a mixture of methanol and water (2 : 1), and concentrated to give 99 g. of a concentrate. To a refluxing solution of 8.2 g. of potassium hydroxide and 80 ml. of iso-
 5 propyl alcohol was added 21 g. of the concentrate under shielding from the light. After 15 minutes, the reaction liquid was poured into 300 ml. of ice-water, made acidic by addition of hydrochloric acid, and extracted with 300 ml. of diethyl ether. The extract was washed with three 100 ml. portions
 10 of water, dried over magnesium sulfate, and evaporated to remove the solvent. The residue was dissolved in 200 ml. of n-hexane and chilled to - 20 °C to crystallize. There was obtained 9.8 g. of the desired product as pale yellow crystals.

15 Analysis for $C_{20}H_{28}O_2$

	C	H
Calculated (%)	79.95	9.39
Found (%)	80.22	9.47

20 NMR spectrum (δ , $CDCl_3$): 1.63 (3H, s), 1.69 (3H, s),
 1.84 (3H, s), 1.99 (3H, s), 2.0 - 2.3 (4H); 2.36
 (3H, s), 5.15 (1H, m), 5.6 - 7.2 (7H, m), 1.04
 (1H, b)

Mass spectrum (m/e): 300 (M^+)

25 Example 4

3,7,11,15,19-Pentamethyl-2,4,6,10,14,18-eicosahexaenoic acid

In 100 ml. of tetrahydrofuran was dissolved 12 g. of
 1-p-tolylsulfonyl-3,7,11,15-tetramethyl-2,6,10,14-hexadeca-
 30 tetraene, and the solution was chilled to - 50 °C. To the
 solution was added dropwise 18.5 ml. of 15 % n-butyllithium-
 - n-hexane solution under stirring and in a stream of nitrogen,
 maintaining the temperature of the solution at - 50 °C.
 Then, 300 ml. of tetrahydrofuran solution containing 5.7 g. of
 35 ethyl 4-bromo-3-methyl-2-butenate was added dropwise to the
 so produced solution. After 30 minutes, 100 ml. of 10 %

0054732

- 13 -

aqueous ammonium chloride solution was added, and then the mixture was allowed to stand to reach room temperature. The mixture was subsequently extracted with two 200 ml. portions of n-hexane. The n-hexane phase was washed with three 100 ml. portions of water, dried over magnesium sulfate, and evaporated to remove the solvent. There was obtained 14 g. of ethyl 3,7,11,15,19-pentamethyl-5-p-tolylsulfonyl-2,6,10,14,18-eicosapentaenoate.

To 4.1 g. of potassium hydroxide in 50 ml. of isopropyl alcohol was added 12 g. of the above-obtained ethyl 3,7,11,15,19-pentamethyl-5-p-tolylsulfonyl-2,6,10,14,18-eicosapentaenoate, and the mixture was stirred at 50 °C for 3 hours. The reaction liquid was poured into ice-water, made acidic by addition of hydrochloric acid, and extracted with 100 ml. of diethyl ether. The extract was washed with water, dried over magnesium sulfate and evaporated to remove the solvent. There was obtained 8.5 g. of an oil. The so obtained oil was dissolved in 40 ml. of n-hexane and chilled to - 20 °C to crystallize. There was obtained 2.3 g. of the desired product as white crystals.

M.p.: 45.5 - 46.5 °C

Analysis for $C_{25}H_{38}O_2$

		C	H
	Calculated (%)	81.03	10.34
25	Found (%)	80.89	10.52
	NMR spectrum (δ , $CDCl_3$): 1.60 (9H, s), 1.68 (3H, s), 1.86 (3H, s), 1.9 - 2.3 (12H), 2.33 (3H, s), 5.09 (3H, b), 5.76 (1H, bs), 5.96 (1H, d, J = 10Hz), 6.18 (1H, d, J = 15Hz), 6.89 (1H, dd, J = 15Hz, 10Hz), 10.2 (1H, b)		

Mass spectrum (m/e): 370 (M^+)

Example 5

Ethyl 3,7,11,15-tetramethyl-2,4,6-hexadecatrienoate

The procedures described in Example 1 were repeated using 6,10,14-trimethyl-3,5-pentadecadien-2-ol to

0054732

- 14 -

obtain the desired product as an oil.

Analysis for $C_{22}H_{38}O_2$

		C	H
	Calculated (%)	78.98	11.45
5	Found (%)	79.16	11.56
	NMR spectrum (δ , $CDCl_3$): 0.87 (9H, d, J = 7Hz), 1.27 (3H, t, J = 7Hz), 0.9 - 1.6 (12H), 1.84 (3H, s), 2.08 (2H, t, J = 7Hz), 2.34 (3H, s), 4.16 (2H, q, J = 7Hz), 5.74 (1H, bs), 5.95 (1H, d, J = 11Hz), 6.16 (1H, d, J = 15Hz), 6.85 (1H, dd, J = 15Hz, 11 Hz)		
10	Mass spectrum (m/e): 334 (M^+)		

Example 6

15 3,7,11,15-Tetramethyl-2,4,6-hexadecatrienoic acid

The procedures described in Example 2 were repeated using the ethyl 3,7,11,15-tetramethyl-2,4,6-hexadecatrienoate obtained in Example 5 to carry out the hydrolysis. There was obtained the desired product as white
20 crystals.

M.p.: 84.5 - 85.5 °C

Analysis for $C_{20}H_{34}O_2$

		C	H
	Calculated (%)	78.38	11.18
25	Found (%)	78.35	11.21
	NMR spectrum (δ , $CDCl_3$): 0.87 (9H, d, J = 7Hz), 0.9 - 1.6 (12H), 1.84 (3H, s), 2.09 (2H, t, J = 7Hz), 2.35 (3H, s), 5.76 (1H, bs), 5.96 (1H, d, J = 11Hz), 6.19 (1H, d, J = 15Hz), 6.90 (1H, dd, J = 15Hz, 11Hz), 11.5 (1H, b)		
30	Mass spectrum (m/e): 306 (M^+)		

Example 7

35 3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoamide

To a suspension of 5.0 g. of 55 % sodium hydride (in oil)

0054732

- 15 -

in 60 ml. of n-hexane was added 28.6 g. of triethyl phospho-
noacetate. The mixture was then heated under reflux, and
20 g. of 6,10,14-trimethyl-3,5,9,13-pentadecatetraen-2-on was
added dropwise to the mixture under stirring. After 30 mi-
5 nutes, the reaction liquid was poured into 200 ml. of ice-
water, and then 500 ml. of n-hexane was added for extraction.
The n-hexane phase was separated, washed with two 100 ml.
portions of a mixture of methanol and water (2 : 1), and con-
centrated. The so obtained concentrate was purified by silica
10 gel column chromatography to give 18 g. of the desired product
as an oil.

To 3.9 g. of potassium hydroxide in 30 ml. of isopropyl
alcohol was added 10 g. of the ethyl 3,7,11,15-tetramethyl-
2,4,6,10,14-hexadecapentaenoate obtained in the
15 above, and the mixture was stirred at 50 °C for 1 hour. The
reaction liquid was poured into ice-water, made acidic by
addition of hydrochloric acid, and extracted with 100 ml. of
diethyl ether. The ether phase was washed with water, dried
over magnesium sulfate and concentrated to give 9.0 g. of an
20 oil. The so obtained oil was dissolved in 50 ml. of n-hexane
and chilled to - 20 °C to crystallize. There was obtained
4.0 g. of 3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic
acid as pale yellow needles.

In 20 ml. of diethyl ether was dissolved 3.0 g. of the
25 above-obtained 3,7,11,15-tetramethyl-2,4,6,10,14-hexadeca-
pentaenoic acid. To this solution was added 1 g. of triethyl-
amine, and further added 1.1 g. of ethyl chlorocarbonate under
stirring at room temperature. After 10 minutes, gaseous
30 ammonia was introduced into the solution. The reaction liquid
was washed with three 10 ml. portions of water, dried over
magnesium sulfate, and evaporated to remove the solvent. The
residue was purified by alumina column chromatography and cry-
stallized from a mixture of acetone and n-hexane (1 : 2). There
35 was obtained 1.7 g. of the desired product as pale yellow
crystals.

0054732

- 16 -

M.p.: 63 - 65 °C

Analysis for $C_{20}H_{31}NO$

	C	H	N
Calculated (%)	79.67	10.37	4.65
5 Found (%)	79.48	10.59	4.73

NMR spectrum (δ , $CDCl_3$): 1.60 (6H, s), 1.68 (3H, s), 1.84 (3H, d, $J = 1\text{Hz}$), 1.9 - 2.3 (8H), 2.33 (3H, d, $J = 1\text{Hz}$), 5.08 (2H, m), 5.70 (1H, bs), 5.4 - 6.1 (2H, b), 5.95 (1H, d, $J = 11\text{Hz}$), 6.15 (1H, d, $J = 15\text{Hz}$), 6.82 (1H, dd, $J = 15\text{Hz}, 11\text{Hz}$)

10 Mass spectrum (m/e): 301 (M^+)

Example 8

15 N-(p-Hydroxyphenyl)-3,7,11,15-tetramethyl-2,4,6,10,14-
hexadecapentaenoamide

In 30 ml. of tetrahydrofuran was dissolved 3 g. of 3,7, 11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoic acid. To this solution was added 1 g. of triethylamine, and further added 1.1 g. of ethyl chlorocarbonate under stirring at room temperature. After 10 minutes, the reaction liquid was poured into 100 ml. of water, and extracted with 100 ml. of n-hexane. The extract was washed with 50 ml. of water and evaporated to remove the solvent. The residue was dissolved in 30 ml. of tetrahydrofuran. To this solution was added 1.1 g. of p-aminophenol, and the mixture was stirred at room temperature for 30 minutes. To the reaction liquid was added 200 ml. of diethyl ether, and the mixture was washed successively with two 50 ml. portions of dilute hydrochloric acid and two 50 ml. portions of water. The ether phase was dried over magnesium sulfate and evaporated to remove the solvent. The residue was crystallized from ethanol to obtain 3.2 g. of the desired product as pale yellow crystals.

M.p.: 163 - 164 °C

Analysis for $C_{26}H_{35}NO_2$

	C	H	N
Calculated (%)	79.34	8.96	3.56
35 Found (%)	79.61	8.78	3.62

0054732

- 17 -

NMR spectrum (δ , CDCl_3): 1.61 (6H, s), 1.68 (3H, s),
 1.85 (3H, s), 1.9 - 2.3 (8H), 2.38 (3H, s), 5.09
 (2H, m), 5.76 (1H, bs), 5.96 (1H, d, $J = 11\text{Hz}$),
 6.15 (1H, d, $J = 15\text{Hz}$), 6.42 (1H, b), 6.74 (2H,
 d, $J = 8\text{Hz}$), 6.82 (1H, d, $J = 15\text{Hz}$, 11Hz), 7.22
 (1H, bs), 7.32 (2H, d, $J = 8\text{Hz}$)

Mass spectrum (m/e): 393 (M^+)

Example 9

N-Ethyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapenta
enoamide

3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoic acid
 and ethylamine were reacted in the same manner as in

Example 8 to obtain the desired product as an oil.

Analysis for $\text{C}_{22}\text{H}_{35}\text{NO}$

	C	H	N
Calculated (%)	80.19	10.71	4.25
Found (%)	80.44	10.79	4.38

NMR spectrum (δ , CDCl_3): 1.15 (3H, t, $J = 7\text{Hz}$), 1.60
 (6H, s), 1.67 (3H, s), 1.83 (3H, s), 1.9 - 2.3
 (8H), 2.33 (3H, d, $J = 1\text{Hz}$), 3.27 (2H, qd, $J =$
 7Hz, 6Hz), 5.10 (2H, m), 5.65 (1H, bs), 5.82
 (1H, t, $J = 6\text{Hz}$), 5.94 (1H, d, $J = 11\text{Hz}$),
 6.10 (1H, d, $J = 15\text{Hz}$), 6.77 (1H, dd, $J =$
 15 Hz, 11Hz)

Mass spectrum (m/e): 329 (M^+)

0054732

- 18 -

Example 10N,N-Dimethyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadeca-
pentaenoate

3,7,11,15-Tetramethyl-2,4,6,10,14-hexadecapentaenoic acid
5 and dimethylamine were reacted in the same manner as in
Example 8 : to obtain the desired product as pale yellow
low crystals.

M.p.: 39 - 39.5 °C

Analysis for $C_{22}H_{35}NO$

10

	C	H	N
Calculated (%)	80.19	10.71	4.25
Found (%)	80.26	10.83	4.32

NMR spectrum (γ , $CDCl_3$): 1.60 (6H, s), 1.68 (3H, s), 1.76
(3H, s), 2.09 (3H, d, J = 1Hz), 1.9 - 2.3 (8H),
15 3.00 (3H, s), 3.01 (3H, s), 5.10 (2H, m), 5.93
(1H, bs), 5.94 (1H, d, J = 10Hz), 6.18 (1H, d,
J = 15Hz), 6.68 (1H, dd, J = 15Hz, 10Hz)

Mass spectrum (m/e): 329 (M^+)

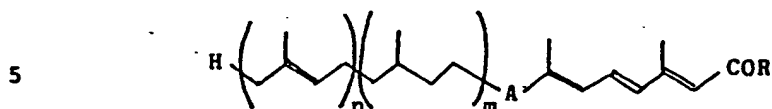
20

0054732

- 19 -

CLAIMS:

1. A conjugated polyprenylcarboxylic acid and its derivative having the formula :



in which each of \underline{n} and \underline{m} is 0, 1 or 2, $n + m$ is 1 or 2, A is

10 , and R is a hydroxyl group, a lower alkoxy group or $-N \begin{smallmatrix} R_1 \\ R_2 \end{smallmatrix}$ wherein each of R_1 and R_2 represents a hydrogen atom, a lower alkyl group, or an aryl group; provided that R is $-N \begin{smallmatrix} R_1 \\ R_2 \end{smallmatrix}$ if A is

15 , \underline{n} is 1 and \underline{m} is 0.

2. A conjugated polyprenylcarboxylic acid as claimed in Claim 1 which is 3,7,11,15,19-pentamethyl-2,4,6,10,14,18-eicosahexaenoic acid.

20 3. A conjugated polyprenylcarboxylic acid as claimed in Claim 1 which is 3,7,11,15-tetramethyl-2,4,6,8,10,14-hexadeca-hexaenoic acid.

25 4. A conjugated polyprenylcarboxylic acid as claimed in Claim 1 which is 3,7,11,15-tetramethyl-2,4,6,14-hexadecatetraenoic acid.

30 5. A conjugated polyprenylcarboxylic acid derivative as claimed in Claim 1 which is N-ethyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoamide.

35 6. A conjugated polyprenylcarboxylic acid derivative as claimed in Claim 1 which is N-p-hydroxyphenyl-3,7,11,15-tetramethyl-2,4,6,10,14-hexadecapentaenoamide.

0054732

- 20 -

7. A pharmaceutical preparation comprising a therapeutically effective amount of a compound according to claim 1, in combination with a carrier or diluent.



European Patent
Office

EUROPEAN SEARCH REPORT

0054732

EP 81 10 9391

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	<p>JOURNAL OF THE CHEMICAL SOCIETY (C), no. 23 (1966) J.B. DAVIS et al. "Carotenoids and related compounds. Part XV" pages 2154-2165</p> <p>* page 2158, comp. XXII; page 2159, comp. XXXIV; page 2161, column 2, last paragraph; page 2164, column 2, 2nd paragraph *</p>	1	<p>C 07 C 57/03 69/587 103/133 A 61 K 31/19 31/23 31/16</p>
X	<p>GB - A - 1 396 622 (RHONE-POULENC)</p> <p>* page 11; example 13 *</p>	1	<p>TECHNICAL FIELDS SEARCHED (Int. Cl. 3)</p> <p>C 07 C 57/00 69/00 A 61 K 31/00</p>
E	<p>FR - A - 2 479 807 (EISAI)</p> <p>* claims 1,5; page 11, lines 1-4 *</p>	1,7	<p>CATEGORY OF CITED DOCUMENTS</p> <p>X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: earlier patent document, but published on, or after the filing date D: document cited in the application L: document cited for other reasons</p>
<p>The present search report has been drawn up for all claims</p>			<p>&: member of the same patent family, corresponding document</p>
Place of search The Hague		Date of completion of the search 23-03-1982	Examiner KLAG

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

☐ **BLACK BORDERS**

☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**

☐ **FADED TEXT OR DRAWING**

☒ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**

☐ **SKEWED/SLANTED IMAGES**

☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**

☐ **GRAY SCALE DOCUMENTS**

☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**

☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**

☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.